CERTIFICATE OF MAILING
37 C.F.R. 1.8

I hereby certify that this correspondence is being deposited with the U.S. Postal Service with sufficient postage as First Class Mail in an envelope addressed to: Assistant Commissioner for Patents, Washington, DC 20231, on the date below:

2/17/2006
Date

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:
Fujise et al.

Serial No.: 10/021,753

Filed: October 30, 2001

For: Methods and Compositions Relating to Fortilin, an Anti-Apoptotic Molecule, and Modulators of Fortilin

Group Art Unit: 1635

Examiner: Angell, Jon E.

Atty. Dkt. No.: UTSH:251US

DECLARATION OF DR. RICK A. WETSEL

UNDER 37 C.F.R. §1.132

Commissioner for Patents
Washington, D.C. 20231

Dear Sir:

I, Rick A. Wetsel, Ph.D., declare the following:

1. I am a Professor in the Research Center for Immunology & Autoimmune Disease and the Director of the Laboratory for Developmental Biology at the University of Texas, Health Science Center in Houston, Texas.

2. My research has been in the general areas of molecule biology and immunology, particularly concerning G-protein coupled receptors. I have published 62 peer reviewed

original scientific publications and 12 invited chapters and review articles. My *curriculum vitae* is attached as Exhibit 1.

3. I am familiar with the level of skill of scientists working in the field of molecular biology, particularly knowledge of assays involving recombinant DNA technology and protein function, as of the October, 2001, which I understand is the priority date of the referenced application.

4. I have reviewed the specification and pending claims 68-83 and 85-87 for the above-referenced case (with the proposed amendment). Claim 68 reads,

> "A method of identifying a modulator of a Fortilin polypeptide comprising:
>
> (a) contacting a candidate modulator with a recombinant cell expressing a Fortilin polypeptide with at least 70% of its amino acids identical or functionally equivalent to SEQ ID NO:2 or that has at least 20 contiguous amino acids from SEQ ID NO:2;
>
> (b) measuring the level of Fortilin activity or expression of the cell; and,
>
> (c) comparing the level of Fortilin activity or expression of the cell to the level of Fortilin activity or expression of a cell not contacted with the candidate modulator,
>
> wherein a difference between the level of Fortilin activity or expression indicates that the candidate modulator is a modulator of a Fortilin polypeptide.

5. A copy of claims 68-83 and 85-87 is attached as Exhibit 2.

6. I understand the Examiner at the United States Patent and Trademark Office has rejected claim 68 (and claims that refer to claim 68) because he contends that "the specification does not appear to have support for a method of identifying a modulator of Fortilin activity using a transfected cell wherein the cell expresses endogenous Fortilin."

7. From reading the specification, it is clear to me that had a person skilled in molecular biology, particularly with knowledge of assays involving recombinant DNA

technology and protein function, read this specification in October of 2001, the specification would have readily described to them the invention described in claim 68. More specifically, the specification indicates that the invention includes screening methods involving recombinant cells that are considered recombinant because they contain exogenous sequences for a number of different nucleic acids, in addition to exogenous Fortilin.

8. This understanding is supported by the specification as a whole, based on passages that include the following:

- *Page 9, lines 1-18*: Specification indicates that screening methods are contemplated to be part of the present invention. It further explains that "this method includes contacting the Fortilin polypeptide with a candidate substance and assaying whether the candidate substance modulates the Fortilin polypeptide."
- *Page 26, lines 18-20*: In another part of the specification, it states, "Determination of which molecules are suitable modulators of Fortilin may be achieved using assays familiar to those of skill in the art—some of which are disclosed herein—and may include, for example, the use of **native** and/or recombinant Fortilin." (Emphasis added).
- *Page 65, line 12-105*: The first sentence in this section states that the "present invention concerns polynucleotides, isolatable from cells, that are free from total genomic DNA and that are capable of expressing all or part of a protein or polypeptide." (Page 65, lines 14-16). This section is directed to nucleic

molecules, such as "Polynucleotides Encoding Native Proteins or Modified Proteins" (page 65, lines 12-13). Significantly, there is a passage that states:

> In particular embodiments, the invention concerns isolated DNA segments and recombinant vectors incorporating DNA sequences that encode a wild-type, polymorphic, or mutant Fortilin or Fortilin modulator polypeptide or peptide that includes within its amino acid sequence a contiguous amino acid sequence in accordance with, or essentially corresponding to a native polypeptide. Thus, an isolated DNA segment or vector containing a DNA segment may encode, for example, a Fortilin modulator that can inhibit or reduce Fortilin activity. (Page

(Page 67, lines 9-15). This passage makes it clear that a Fortilin modulator may be recombinant. Additionally, this section of the application also includes a discussion of vectors starting at page 72, which also describes various promoters such as "recombinant or heterologous promoter" (page 73, lines 26-29). Moreover, this section also includes a discussion of "host cells" in which it is stated that "a host cell may be 'transfected' or 'transformed, which refers to a process by which exogenous nucleic acid, such as a modified protein-encoding sequence, is transferred or introduced into a host cell." (Page 84, lines 20-30). Such a host cell would be considered a "recombinant" cell.

- *Page 106, line 19-page 110-, line 29*: This section is entitled " Screening Methods Involving FORTILIN," and it describes how to identify a Fortilin modulator. It states, "one generally will determine the activity or level of inhibition of Fortilin in the presence and absence of the candidate substance, wherein a modulator is defined as any substance that alters these characteristics. For example, a method generally comprises: (a) providing a candidate modulator; (b) admixing the candidate modulator with an isolated compound or cell expressing the compound; (c) measuring one or more characteristics of the

compound or cell in step (b); and (d) comparing the characteristic measured in step (c) with the characteristic of the compound or cell in the absence of said candidate modulator, wherein a difference between the measured characteristics indicates that said candidate modulator is, indeed, a modulator of the compound or cell." (Page 106, line 27-page 107, line 11). It also states how "[a]ssays may be conducted in cell free systems, in isolated cells, or in organisms including transgenic animals." (Page 107, lines 13-14). The cells of such transgenic animals could be considered recombinant cells; moreover, this passage does not limit transgenic animals to those that express only an exogenous Fortilin polypeptide.

- *Page 159-160*: In Example 9, experiments are described involving a recombinant cell (cell transfected with two different plasmids) that expresses GAL4-DNA-BD (binding domain)-Fortilin and VP16-DNA-AD (activating domain)-p53. In addition to expressing exogenous Fortilin, these cells express other nucleic acids that are exogenous to the cells and thus, the cell can be considered "recombinant" by virtue of being transfected with other non-Fortilin nucleic acids sequences.

9. These cited passages make it clear to me that the patent application describes what is recited in claim 68, in particular, the use of a recombinant cell expressing Fortilin polypeptide in a method of screening for Fortilin modulators. This includes cells that are recombinant because they express exogenous nucleic acids other than exogenous Fortilin. Moreover, the specification makes clear that the cell may express native Fortilin as well. *See* page 26, lines 18-20.

10. I hereby declare that all statements made of my own knowledge are true and all statements made on information are believed to be true and further that the statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment or both under § 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of this application or any patent issued thereon.

February 7, 2006
Date

Rick A. Wetsel
Rick A. Wetsel, Ph.D.

Exhibit 1

Principal Investigator/Program Director (Last, First, Middle): Wetsel, Rick, A

BIOGRAPHICAL SKETCH

Provide the following information for the key personnel and other significant contributors in the order listed on Form Page 2.
Follow this format for each person. DO NOT EXCEED FOUR PAGES.

NAME	POSITION TITLE
Rick A. Wetsel, Ph.D.	Professor of Molecular Medicine
eRA COMMONS USER NAME RWETSE	

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, and include postdoctoral training.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	YEAR(s)	FIELD OF STUDY
University of Texas at Austin	B.S.	1976	Chemistry
University of Texas Health Science Center at San Antonio	Ph.D.	1982	Biochemistry
Scripps Research Institute, La Jolla, CA	Postdoctoral	1983-1986	Immunology/Mol Biol

PROFESSIONAL POSITIONS:

1986-1996 Assistant Professor of Pediatrics and Assistant Professor of Molecular Microbiology, Washington University School of Medicine, Department of Pediatrics, St. Louis, Missouri
1992 Visiting Investigator, Basel Institute for Immunology, Basel, Switzerland
1996-2001 Associate Professor, Research Center for Immunology and Autoimmune Diseases, Institute of Molecular Medicine for the Prevention of Human Diseases, University of Texas-Houston, Houston, Texas; Director, Laboratory for Developmental Biology
2001-Present Professor, Research Center for Immunology and Autoimmune Diseases, Institute of Molecular Medicine for the Prevention of Human Diseases, University of Texas-Houston; Director, Laboratory for Developmental Biology

AWARDS & OTHER PROFESSIONAL ACTIVITIES:

1981 Mead Johnson Excellence of Research Award
1981 James W. McLaughlin Award in Infectious Disease and Immunology
1989-1994 Research Career Development Award, NIH
1995 National Institute of Arthritis and Musculoskeletal and Skin Diseases - Program Project Review Committee
1995-2000 Associate Editor, *Journal of Immunology*
1996-1999 National Institute of Allergy and Infectious Diseases-Allergy, Immunology, and Transplantation Research Committee; Ad Hoc Grant Reviewer
1998 Member of Special Emphasis Panel Immunobiology Study Section
1998 Member of Special Study Section, NIAID, National Institutes of Health
1999 Immunological Sciences Study Section, NIAID; Ad Hoc Reviewer
1999,2001 Biophysical and Chemical Sciences Initial Review Group
2000-2002 Arthritis Foundation, Member, Inflammation Study Section
2000-2002 American Heart Association, Member, Peer Review Committee 3A
2002-2004 Council, International Complement Society
2002-2003 Arthritis Foundation, Vice-Chair, Inflammation Study Section
2003-2004 Allergy & Immunology Study Section, NIAID, Member
2004-Present Treasurer, International Complement Society
2004-Present Arthritis Foundation, Chair, Inflammation Study Section
2004-Present Innate Immunity and Inflammation Study

RECENT PUBLICATIONS (Selected from 74):

Singer L, Whitehead WT, Akama H, Katz Y, Fishelson Z, **Wetsel RA**: Inherited human complement C3 deficiency: An amino acid substitution in the α-chain (Asp549 to Asn) impairs C3 secretion. J. Biol. Chem. 1994; 269:28494-28499.

Katz Y, **Wetsel RA**, Schlesinger MD, Fishelson Z: Compound heterozygous complement C3 deficiency. Immunology 1995; 94:5-7.

Wetsel RA: Expression of the C5a anaphylatoxin receptor (C5aR) on non-myeloid cells. Immunol. Lett. 1995; 44:183-187.

Haviland DL, McCoy RL, Whitehead WT, Akama H, Molmenti EP, Brown A, Parks WC, Perlmutter DH, **Wetsel RA**: Cellular expression of the C5a anaphylatoxin receptor (C5aR): Demonstration of C5aR on non-myeloid cells of the liver and lung. J. Immunol. 1995; 154:1861-1869.

Wang X, Fleischer DT, Whitehead WT, Haviland DL, Rosenfeld SI, Leddy JP, Snyderman R, **Wetsel RA**: Inherited human complement C5 deficiency: Nonsense mutations in exons 1 (Gln1 to Stop) and 36 (Arg1458 to Stop) and compound heterozygosity in three African-American families. J. Immunol. 1995; 154: 5464-5471.

McCoy RL, Haviland DL, Molmenti EP, Ziambaras T, **Wetsel RA**, Perlmutter DH: The N-formylpeptide and complement C5a receptors are expressed in liver cells and mediate hepatic acute phase gene regulation. J. Exp. Med. 1995; 182:207-217.

Lacy M, Jones J, Whittlemore SR, Haviland DL, **Wetsel RA**, Barnum SR: Expression of the receptors for the C5a anaphylatoxin, interleukin-8 and fMLP by human astrocytes and microglia. J. Neuroimmunol. 1995; 61:71-78.

Wetsel RA, Kulics J, Lokki M-J, Kiepiela P, Akama H, Johnson CAC, Densen P, Colten HR: Type II human complement C2 deficiency: Allele-specific amino acid substitutions (Ser189 to Phe; Gly444 to Arg) cause impaired C2 secretion. J. Biol. Chem. 1996; 271:5824-5831.

Singer L, Van Hee ML, Lokki M-J, Kramer J, Borzy MS, **Wetsel RA**: Inherited complement C3 deficiency: Reduced C3 mRNA and protein levels in a Laotian kindred. Clin. Immunol. Immunopath. 1996; 81:244-252.

Stahl PF, Frei K, Eugster H-P, Fontana A, Hummel KM, **Wetsel RA**, Ames RS, Barnum SR: TNF-α-mediated expression of the receptor for anaphylatoxin C5a (C5aR) on neurons in experimental listera meningoencephalitis. J. Immunol. 1997; 159:861-869.

Hollmann TJ, Haviland DL, Kildsgaard J, Watts K, **Wetsel RA**: Cloning, expression, sequence determination, and chromosome localization of the mouse complement C3a anaphylatoxin receptor gene. Molec. Immunol. 1998; 35:137-148.

Wang X, Circolo A, Lokki M-J, Shackelford PG, **Wetsel RA**, Colten HR: Molecular heterogeneity in deficiency of complement protein C2 type I. Immunology 1998; 93:184-191.

Circolo A, Garnier G, Fukuda W, Wang X, Hidvegi T, Szalai AJ, Briles DE, Volanakis JE, **Wetsel RA**, Colten HR. Genetic disruption of the murine complement C3 promoter region generates C3 deficient mice. Immunopharmacology 1999; 42: 135-149.

Wetsel RA, Kildsgaard J, Zsigmond E, Liao W, Chan L. Genetic deficiency of acylation stimulating protein (ASP/C3adesArg) does not cause hyperapobetalipoproteinemia in mice. J Biol Chem 1999; 274: 19429-19433.

Wetsel RA, Kildsgaard J, Haviland DL: Complement anaphylatoxins (C3a, C4a, C5a) and their receptors (C3aR, C5aR/CD88) as therapeutic targets in inflammation. In: "Therapeutic interventions in the Complement System". J Lambris and MV Holers, editors, Human Press, Totowa, NJ, 2000; Chpt. 5:113-154.

Watanabe H, Garnier G, Circolo A, **Wetsel RA**, Ruiz P, Holers VM, Boackle SA, Colten HR, Gilkeson GS: Modulation of renal disease in MRL/lpr mice genetically deficient in the alternative complement pathway factor B. J Immunol 2000; 164:786-794.

Kildsgaard J, Hollmann TJ, Matthews KW, Bian K, Murad F, **Wetsel RA**: Cutting Edge: Targeted disruption of the C3a receptor gene demonstrates a novel protective anti-inflammatory role for C3a in endotoxin-shock. J Immunol 2000; 165:5406-5409.

Drouin SM, Kildsgaard J, Haviland J, Zabner J, Jia HP, McCray PB, Tack BF, **Wetsel RA**: Expression of the complement anaphylatoxin C3a and C5a receptors on bronchial epithelial and smooth muscle cells in models of sepsis and asthma. J Immunol 2001; 166:2025-2032.

Nataf S, Carroll SL, **Wetsel RA**, Szalai AJ, Barnum SR. Attenuation of experimental autoimmune demyelination in complement-deficient mice. J Immunol 2000; 165:5867-5873.

Matthews KW, **Wetsel RA**. Characterization of the mouse carboxypeptidase N small active subunit gene structure. J. Immunol. 2001; 166:6196-6202.

Drouin SM, Corry DB, Kildsgaard J, **Wetsel RA**. Cutting Edge: The absence of C3 demonstrates a role for complement in Th2 effector functions in a murine model of pulmonary allergy. J Immunol 2001; 167:4141-4146.

Drouin SM, Corry DB, Hollmann TJ, Kildsgaard J, **Wetsel RA**. Absence of the complement C3a receptor suppresses Th2 effector functions in a murine model of pulmonary allergy. J Immunol 2002, 169:5926-5933..

Lawrenz MB, Wooten RM, Zachary JF, Drouin SM, Weis JJ, **Wetsel RA**, Norris SJ. Effect of complement component C3 deficiency on experimental Lyme borreliosis in mice. Infect Immun 2003; 8:4432-4440.

Girardi G, Berman J, Redecha P, Spruce L, Thurman JM, Kraus D, Hollmann TJ, Casali P, Carroll MC, **Wetsel RA**, Lambris JD, Holers VM, Salmon JE. Complement C5a receptors and neutrophils mediate fetal injury in the antiphospholipid syndrome. J Clin Invest 2003; 112:1644-1654.

Riedemann NC, Gao R-F, Hollmann TJ, Gao H, Neff TA, Reuben J, Speyer CL, Sarma VJ, Zetoune FS, **Wetsel RA**, Ward PA. Regulatory role of C5a for LPS-induced IL-6 production in neutrophils during sepsis. FASEB J 2004; 18:370-372.

Matthews KW, Drouin SM, Liu C, Martin JF, Skidgel R, **Wetsel RA**. Expression of the third complement component (C3) and carboxypeptidase N small subunit (CPN1) during mouse embryonic development. Develop Comp Immunol 2004, 28:647-655.

Ratajczak J, Reca R, Kucia M, Majka M, Allendorf DJ, Baran JT, Janowska-Wieczorek A, **Wetsel RA**, Ross GD, Ratajczak MZ. Mobilization studies in mice deficient in either C3 or C3a-receptor (C3aR) reveal a novel role for complement in retention of hematopoietic stem/progenitor cells in bone marrow. Blood 2004, 103:2071-2078.

Mueller-Ortiz S, Drouin SM, **Wetsel RA**. The alternative activation pathway and complement component C3 are critical for a protective immune response against *Pseudomonas aeruginosa* in a murine model of pneumonia. Infect Immun 2004, 72:2899-2906.

Lee LY, Hook M, Haviland DL, **Wetsel RA**, Yonter EO, Synbegs P, Vernachio J, Brown EL. Inhibition of complement activation by a secreted staphylococcus aureus protein. J Infect Dis 2004, 190:571-579.

Reidemann NC, Guo RF, Guo H, Sun L, Hoesel M, Hollmann TJ, **Wetsel RA**, Zetonne FS, Ward PA. Regulatory role of C5a on macrophage migration inhibitory factor release from neutrophils. J Immunol 2004, 173:1355-1359.

Markiewski MM, Mastellos D, Tudoran R, DeAngelis RA, Strey CW, Franchini S, **Wetsel RA**, Erdei A, Lambris JD. C3a and C3b activation products of the third component of complement (C3) are critical for normal liver recovery after toxic injury. J Immunol 2004, 173:747-754.

Boos L, Campbell IL, Ames R, **Wetsel RA**, Barnum SR. Deletion of the complement anaphylatoxin C3a receptor attenuates, whereas ectopic expression of C3a in the brain exacerbates, experimental autoimmune encephalomyelitis. J Immunol 2004; 173:4708-4714.

RESEARCH PROJECTS ONGOING OR COMPLETED DURING THE LAST 3 YEARS:

ONGOING

5 R01 AI 25011-12 (Wetsel) 07/01/87 – 02/28/06 40%
NIH/NIAID $200,000
Complement Anaphylatoxin Receptors in Inflammation
The goal of this research program is to increase our understanding of the specific and overall roles that complement anaphylatoxins and their receptors play in inflammation and immunity by using C3aR and C5aR "knock-out" mice in various disease models. The current proposal is a renewal of this grant award.

R01 HL 074333-02 (Wetsel) 07/10/03 – 06/30/07 30%
NIH/NHLBI $225,000
Complement in Allergic Lung Disease
The main focus of this research is to delineate the overall contribution and potential mechanisms that complement utilizes to mediate the pathogenesis of allergic lung disease. The results from this study will facilitate the evaluation of complement as a therapeutic target in the treatment of asthma.

R01 HL68520 (Jagannath) 09/30/01 – 07/31/06 10%
Reactivation tuberculosis in A/J mice $250,000
The major goal of this project is to characterize latent tuberculosis in complement C5 deficient A/J mice. There is no overlap with the current proposal.

T32 DK061929 09/30/02-09/29/07
NIH Institutional National Research
Service Award
Postdoctoral training in renal diseases and hypertension

COMPLETED

5 R01 AI25011 (Wetsel) 07/01/87 – 06/30/00 40%
NIH/NIAID
Complement C5 and the C5a-Receptor: Molecular Genetics
The long term objective of this project is to understand and thereby selectively modulate the inflammatory and cytolytic effects resulting from C5 activation, so that tissue damage mediated by C5 activation polypeptides in the pathogenesis of certain diseases can be abrogated.

9950394N (Wetsel) 01/01/99 – 12/31/01 10%
AHA National Grant-in-Aid
Complement and the Development of Atherosclerosis
The long term objective of this project is to determine complement's role in the initiation and perpetuation of atherosclerosis. Studies are carried out using C3 and ApoE "knock-out" mice.

5 F32 AI10223 (Drouin) 09/01/99 – 08/31/02 0%(sponsor)
NIH/NIAID $40,036
Molecular Analysis of the Complement C3a Receptor
The long term objective of this proposal is to delineate the structure/functional relationships of the human G protein-coupled C3a anaphylatoxin receptor by expression and mutagenesis studies.

Exhibit 2

68. (currently amended) A method of identifying a modulator of a Fortilin polypeptide comprising:

(a) contacting a candidate modulator with a recombinant cell expressing a Fortilin polypeptide with [that is] at least 70% of its amino acids identical or functionally equivalent to SEQ ID NO:2 or that has at least 20 contiguous amino acids from SEQ ID NO:2;

(b) measuring the level of Fortilin activity or expression of the cell; and,

(c) comparing the level of Fortilin activity or expression of the cell to the level of Fortilin activity or expression of a cell not contacted with the candidate modulator,

wherein a difference between the level of Fortilin activity or expression indicates that the candidate modulator is a modulator of a Fortilin polypeptide.

69. (previously presented) The method of claim 68, wherein the level of Fortilin activity is measured.

70. (previously presented)The method of claim 69, wherein the Fortilin activity is protein binding.

71. (previously presented) The method of claim 70, wherein the Fortilin activity is p53 binding.

72. (previously presented) The method of claim 69, wherein the Fortilin activity is MCL1 binding.

73. (previously presented)The method of claim 69, wherein the Fortilin activity is cell cycle progression.

74. (previously presented) The method of claim 69, wherein the Fortilin activity is prevention of apoptosis.

75. (previously presented) The method of claim 68, wherein the level of Fortilin expression is measured.

76. (previously presented) The method of claim 75, wherein the level of Fortilin polypeptide is measured.

77. (previously presented) The method of claim 75, wherein the level of Fortilin mRNA is measured.

78. (previously presented) The method of claim 75, wherein Fortilin half-life is measured.

79. (previously presented) The method of claim 68, wherein the candidate substance is a polypeptide.

80. (previously presented) The method of claim 79, wherein the polypeptide is an antibody.

81. (previously presented) The method of claim 68, wherein the candidate substance is a nucleic acid.

82. (previously presented) The method of claim 81, wherein the nucleic acid comprises at least 20 contiguous nucleotides identical or complementary to SEQ ID NO:1.

83. (previously presented) The method of claim 68, wherein the candidate substance is a small molecule.

85. (previously presented) The method of claim 84, wherein the mammalian polypeptide is a human Fortilin polypeptide.

86. (previously presented) The method of claim 68, wherein the Fortilin polypeptide is a mammalian Fortilin polypeptide.

87. (previously presented) The method of claim 86, wherein the mammalian polypeptide is a human Fortilin polypeptide.